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FOR

COSMETIC OR DERMATOLOGICAL COMPOSITIN CONTAINING AN ACTIVE AGENT WHICH STIMULATES SYNTHESIS OF THE PROTEIN HSP 32 IN THE SKIN, AND COSMETIC TREATMENT METHOD

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COSMETIC OR DERMATOLOGICAL COMPOSITION CONTAINING AN ACTIVE AGENT WHICH STIMULATES SYNTHESIS OF THE PROTEIN HSP 32 IN THE SKIN, AND COSMETIC TREATMENT METHOD

The present invention relates to compositions, in particular dermato-cosmetological compositions, which are useful in the field of photoprotection, and to cosmetic methods for treating skin exposed to solar radiation.

Solar radiation, and mainly ultraviolet radiation, can cause harmful phenomena in the medium or long term. The solar energy reaching the ground is distributed, at wavelengths (λ) from 290 to 2 500 nm, for 50% in the infrared region (λ = 800 to 2 500 nm), 40% in the visible region (λ = 400 to 800 nm) and for 10% in the ultraviolet region, in which a distinction is made between the UVA region (λ = 320-400 nm) and the UVB region (λ = 290-320 nm).

Although immediate (UVA) or delayed (UVB) pigmentation constitutes a natural means of defense of the skin, exposure to ultraviolet radiation may cause actinic erythema, epidermal hyperplasia, cutaneous senescence (or solar elastosis) and even, in certain cases, may promote the onset of skin cancers.

Although the majority of the UVB radiation is absorbed by the horny layer, 10% reaches the dermis; the majority of the UVA radiation (and some of the visible radiation) crosses the epidermis and 20 to 30% reaches the dermis, where it may cause adverse changes in the skin cells.

It is accepted that UVA radiation causes the production of reactive oxygen species, in particular via the intracellular generation of H_2O_2 (Morlière et al., 1992).

The compounds have many target cells and cause various types of damage:

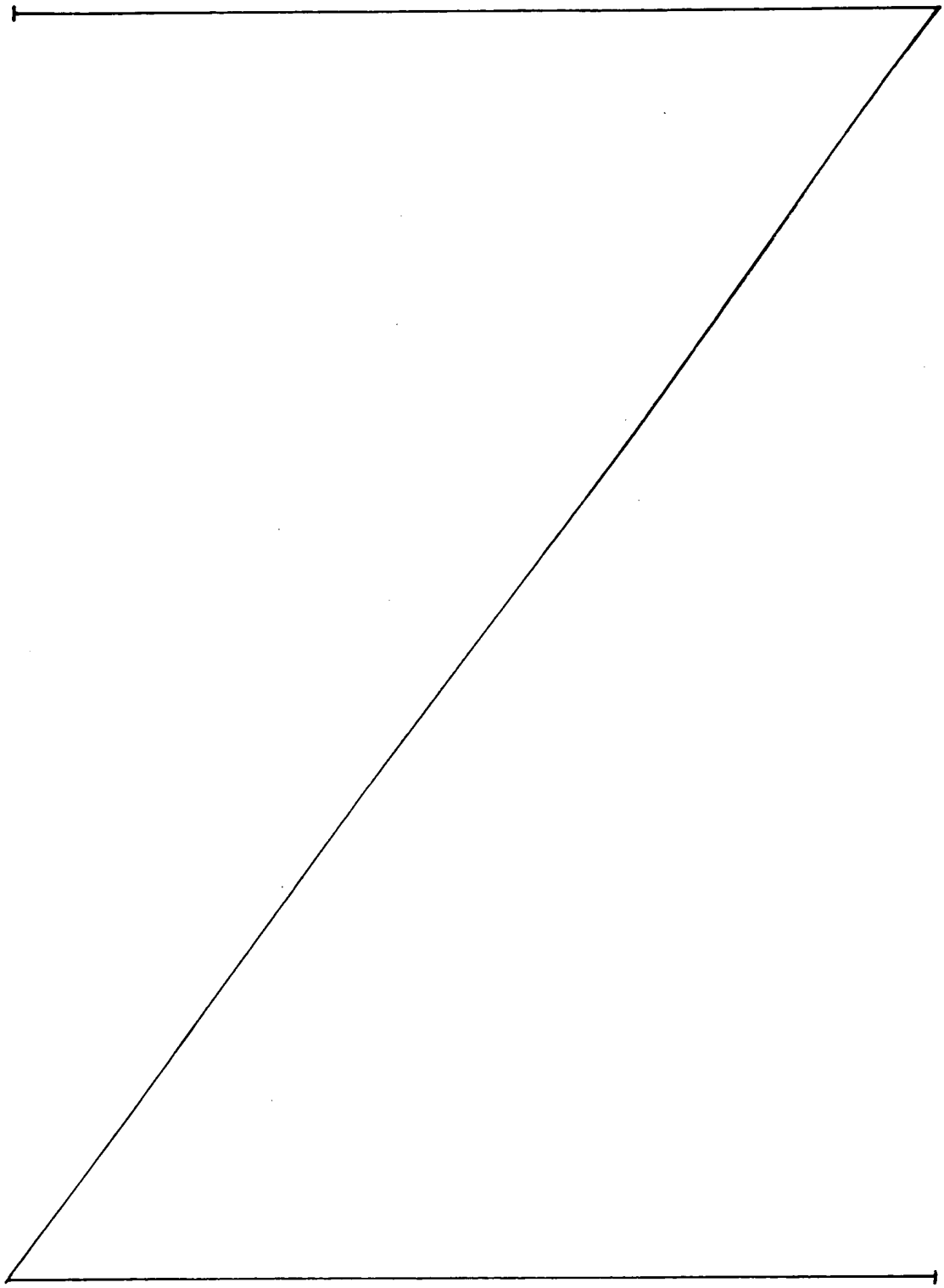
- DNA: single- or double-strand cleavages, DNA-protein bridging,
- proteins: singlet oxygen reacts with certain residues, including histidine and tryptophan,
- membranes: peroxidation of polyethylenic fatty acids.

These adverse changes take place on all types of skin cells, in particular keratinocytes, melanocytes and fibroblasts, and are generally inflammatory manifestations or manifestations of actinic ageing (wrinkles).

It is also acknowledged that "HSPs" ("heat shock proteins") have been demonstrated on cells, both eukaryotic and prokaryotic cells, subjected to physiological stress, in particular heat stress, both in vivo and in vitro. These cells react by expressing a set of proteins which vary in number and size depending on the target organism and the inducing stress (Maytin, 1995; Milarski et al., 1989).

HSPs are classed in families according to their molecular weight. HSP 90, HSP 70, HSP 60 and HSP 30 have thus been distinguished. Many of the genes encoding the HSPs have been sequenced and their chromosomal location determined; however, little information is currently available regarding the transcriptional control of these molecules which are suspected of being among the cellular devices for protecting against a toxic environment.

Many factors may cause the induction of HSPs: high temperatures, heavy metals, viral infections, alcohol, growth factors and low temperatures (Simon et al.,



Advantageously, the compositions according to the invention contain at least one UVA-ray and/or UVB-ray screening agent. These screening agents are well known to those skilled in the art. Mention may be made, for

example, of benzophenones, such as 2,2',4,4'-tetrahydroxybenzophenone or Benzophenone-2 and 2-hydroxy-4'-methoxybenzophenone or Eusolex 4360®, which absorbs UVA and UVB radiation, cinnamate derivatives such as octyl p-methoxycinnamate or Parsol MCX®, which absorbs UVB radiation, dibenzoylmethane derivatives such as 4-tert-butyl-4'-methoxydibenzoylmethane or Parsol 1789®, which absorbs UVA radiation, and para-aminobenzoic acid (Paba) esters, such as octyldimethyl PABA or Escalol 507®, which absorbs UVB radiation.

In this regard, it is important to note that the fibroblasts, which are major cells of the dermis giving the skin its tonicity, are the only skin cells in which it is particularly advantageous to induce the production of the protein HSP 32. It is thus particularly advantageous, in order to restore or conserve a good physiological condition of the skin, to stimulate the formation of this protein by the fibroblasts.

Consequently, the present invention also relates to the use of a compound capable of activating the endogenous synthesis of HSP 32, for the preparation of a cosmetic composition for protecting fibroblasts. Among the compounds described in the prior art which are capable of activating the synthesis of HSPs in general, mention should be made of patent application FR 2 757 863 which describes the use of biological substances of plant origin extracted from the fruit of plants with CAM metabolism.

Among the compounds capable of promoting the endogenous production of HSP 32 by the fibroblasts, mention may be made of caffeic acid esters and derivatives thereof, in particular oraposide which has been described in documents WO 92/16544, FR 2 652 086, FR 2 708 851 and FR 2 699 818, and also PCOs (procyanidol oligomers)

which have been described in documents EP 953 353, EP 955 051 and EP 397 914 and the article by J. Masquelier (1990, Parfums, cosmétiques, arômes No. 95, pp. 89-97) and which may be extracted from grape and from green tea, for example, and also derivatives thereof.

Among the PCO derivatives which may be used, mention should also be made of the crosslinked PCOs as described in patent US 5 780 060.

The compounds according to the present invention will preferably be used at concentrations of between 0.1% and 5% by weight of the composition and preferably at concentrations of between 0.2% and 1% by weight.

The compositions according to the present invention may comprise combinations of several "activating" compounds, as well as combinations with other advantageous components.

Among the preferred combinations, mention should be made more particularly of those which contain at least one compound chosen from:

- forskolin or any extract containing it, in particular extracts of Plecthantrus barbatus,
- tyrosine and its derivatives, in particular malyltyrosine,
- ellagic acid and its derivatives or any extract containing them,
- extracts of Centella asiatica, of Potentilla erecta and of Eriobotrya japonica,
- soybean saponins and alfalfa saponins such as soyasapogenols,
- isoflavones, in particular formononetin, daidzein and genistein or mixture thereof,
- vitamin C and its derivatives, in particular vitamin C magnesium phosphate, tocopherol and its

esters, in particular tocopheryl gentisate and tocopheryl phosphate,
- 18-β-glycyrrhetinic acid,
- extracts of Azadiracta indica,
- curcuminoids, in particular a curcumin.

It is advantageous to note that the compositions according to the present invention can also contain heat shock proteins, in particular the protein HSP 32 itself or an active fragment thereof.

Preferably, the compositions according to the present invention will be in a form which is suitable for topical cutaneous administration.

These compositions may especially be in the form of solutions, suspensions, lotions, milks, gels, creams, O/W or W/O emulsions or multiple emulsions, sticks or powders, suitable for application to the skin, the lips and/or the hair.

They comprise the excipients required for this formulation, such as solvents, diluents, thickeners, ionic or nonionic surfactants, in particular sucroesters, preserving agents, antioxidants, colorants, fragrances or, when they are packaged as aerosols, propellant gases.

The compositions may also contain softeners, moisturizers, anti-inflammatory agents, anti-wrinkle agents, in particular agents promoting the synthesis of glycosamino-glycan (GAG), or tanning activators.

Advantageously, the compositions according to the invention contain a free-radical scavenger, for example α-tocopherol or its esters.

According to one of the embodiments of the invention, the composition also contains at least one photoprotective agent, preferably chosen from the group consisting of physical sunblocks and sunscreens.

Sunscreens are molecules capable of absorbing radiation within a more or less broad region of the solar spectrum. They may belong to various classes; mention may be made, in a non-limiting manner, of para-aminobenzoic acid and its derivatives, cinnamic acid esters, salicylic acid derivatives or benzylidenecamphor derivatives, benzimidazoles and benzophenone derivatives.

The physical sunblocks which may be used are, in particular, titanium oxide, zinc oxide, mica derivatives and talc.

The presence of physical sunblocks or sunscreens in the composition will make it possible to improve the protection against solar radiation of the body surface onto which it is applied.

A subject of the invention is also the use of at least one compound chosen from the group consisting of PCOs and derivatives thereof, caffeic acid esters and derivatives thereof and mixtures of these compounds, for the preparation of a composition intended to activate the endogenous synthesis of HSP 32 or a functional peptide fragment of such a protein.

The preferential aspects stated above for the composition per se are also valid for the composition prepared and intended to activate the endogenous synthesis of HSP 32 or a functional peptide fragment of such a protein according to this use. In particular, the use according to the invention is characerized in

that the composition contains pharmaceutically and/or cosmetologically acceptable excipients.

Another subject of the invention is a cosmetic method for treating the skin and integuments in order to protect them against the harmful effects of radiation, in particular ultraviolet radiation, characterized in that an effective amount of a composition as described above is applied locally, before or at the time of exposure to radiation, in particular ultraviolet radiation, for example solar radiation.

More particularly, the above method is intended to combat the formation of solar erythema, solar allergies or solar elastosis and to prevent or delay the appearance of wrinkles caused by the harmful effects of ultraviolet radiation.

Finally, according to another of its aspects, the invention comprises the use of these compositions as medicinal products, in particular in dermatology.

A subject of the invention is also the application, as a cosmetic product, of the heat shock protein HSP 32.

In the examples which follow, the protective effect of PCOs by means of inducing HSP 32 will be demonstrated as a function of an administration or otherwise of UVA.

EXAMPLE 1

The following examples were carried out using fibroblast cell cultures which are or are not subjected to the treatment with PCOs and then on which, after UVA radiation, the induction of HSP 32 is assayed by means known to those skilled in the art.

These means in particular comprise the use of an anti-HSP 32 primary antibody, commercially available from

the company TEBU, in a technique known as immunodetection.

The results obtained are collated in the table below.

Effect of PCO on the expression of the protein HSP 32 with or without UVA (Western blot)

	CONTROL		PCO 25 μg/ml		PCO 50 μg/ml	
	UV -	UV +	UV -	UV +	UV -	UV +
Volume density	95 832	125 208	140 935	123 165	163 328	195 552
Effect/control UV-	100%	131%	147%	128%	170%	204%

It is found that the UVA naturally induces the synthesis of HSP 32 (protein quantified by Western blot) but this synthesis remains moderate. The addition of PCO stimulates the induction of the HSP 32 molecules more strongly than UVA alone, in particular when the PCOs are used at 50 μg/ml.

Treating the cells with PCOs followed by UVA irradiation leads to a massive stimulation of the production of HSP since it may be up to 204% when the PCOs are used at 50 μg/ml.

The protective effect of these PCOs is thus clearly demonstrated, both with and without irradiation. Thus, the compositions may be used preventively and/or curatively, preferably in combination with UVA-stabilizing and/or UVB-stabilizing screening agents.

- Extract of Centella asiatica	0.5
- Octyl methoxycinnamate	2
- Excipient, qs	100

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